Recent Advances in Fibre Tracking

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1. Introduction

Fibre tracking, or tractography, using diffusion MRI information is unique in its ability to estimate the trajectories of white matter fibre bundles non-invasively. Diffusion weighted MRI (DWI) allows information regarding the orientation of axonal bundles to be encoded in each voxel of an MR image (typically, but not necessarily, an echo planar image). This voxel-by-voxel information provides estimates of the dominant fibre bundle orientations, which may then be extrapolated to provide estimates of the routes of inter-voxel, and hence inter-regional, fibre bundle connections. Fibre tracking is therefore a tool that allows two basic experiments to be performed: First, it is a segmentation method for isolating the white matter tracts within the brain. This is of potential interest to those who wish to identify *functionally-relevant* areas of white matter – white matter structures associated with a particular functional network (for example, the tracts of the motor system). Second, it is a method to identify those areas of the brain that are connected to each other via white matter tracts. This is of interest to those who wish to understand normal neuroanatomy and the effects of disease and abnormality (for example, disconnection within a network subsequent to infarction in the white matter).

This document first provides a brief summary of the main methods of fibre tracking. Application of tractography in situations of complex fibre architecture (crossing fibres, etc) is then explored, followed by a discussion of examples of the application of fibre tracking to allow quantitative measurements in the brain.

2. Fibre Tracking Methods

Diffusion weighted MRI data, once suitably processed, provides information regarding fibre orientation in each image voxel. This information is present either as vectors representing dominant fibre bundle orientations or as continuous functions on the sphere representing the evidence for the presence of fibres at any given angle.

2.1. 'Streamline' Methods

The best-established approach to the problem of tractography exploits the close analogy between the fibre orientation vector field in the brain and flow vector fields in fluid dynamics (1, 2). Tractography 'streamlines' typically utilise the principal eigenvector ($\boldsymbol{\varepsilon}_1$) of the diffusion tensor to provide a propagation direction for each voxel along the path, as it is generally accepted that $\boldsymbol{\varepsilon}_1$ is collinear with the principal orientation of fibre bundles when the tensor is an adequate model of tissue structure and noise is negligible (3). The process of streamline generation is then essentially a process of following the local vector information step-by-step until a full trajectory is created. Figure 1 shows an example of streamlines used to isolate the superior longitudinal fasciculus (using the methods presented in Catani *et al* (4)).

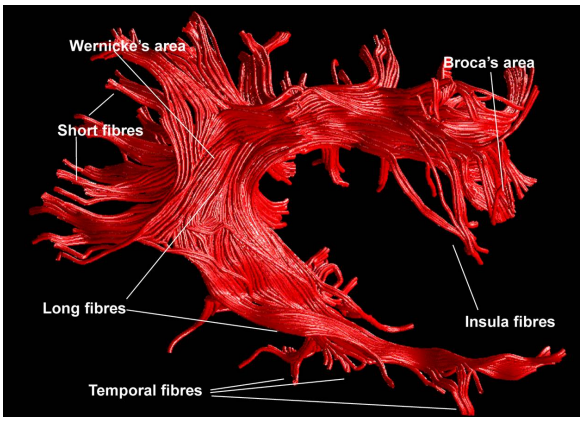

Figure 1. Streamline reconstruction of the superior longitudinal fasciculus (image courtesy Derek Jones).

2.2. Distributed Connection Methods

Streamline methods generally provide a single route of connection through any given point in the brain. A number of methods have been proposed to provide more distributed patterns of connection to any point. These approaches have two main advantages: First, they have a natural ability to characterise branching structures in the brain (as seen, for example, in the corona radiata). Whilst it is possible to create the impression of branching by using large numbers of densely-packed tracking start points when using streamlines (Fig. 1), it remains an essentially 'point-to-point' tracking method. Second, distributed tracking techniques provide a measure of the *degree* of inter-connection between voxels and brain regions, something that streamline methods cannot provide.

A number of distributed tracking methods have been proposed (5-10). For example, attempts have been made to assess cerebral connections by using a simulated particle 'random walk' diffusion process, driven by the orientational diffusion characteristics measured in each voxel, with the aim of establishing patterns of connection in a distributed manner using Monte Carlo methods (5, 11, 6, 12). This process is allowed to continue until the random walk has reached some stopping criterion and each voxel in the brain encountered on the random walk is noted. This

is then repeated a large number of times and the frequency over all repeats at which any voxel in the brain is encountered by the random walk provides an index of the 'degree of connection' from the start point to that voxel.

Other distributed tracking approaches include front evolution methods (13, 8, 14). These methods propagate a wavefront through the directional information provided using DWI, and differ from the Monte Carlo approaches in that the evolution of the front is deterministic rather than statistical. However, in common with the results of the Monte Carlo methods discussed above, front evolution methods generate maps of a distributed 'degree of connection' index. Figure 2 shows an example of such a map, generated with the 'fast marching tractography' (FMT) method (13, 15, 16, 8).

Although distributed tracking methods generally provide some form of ranking of how much credence to give any identified connection, the exact interpretation of the 'degree of connection' varies considerably from method to method.

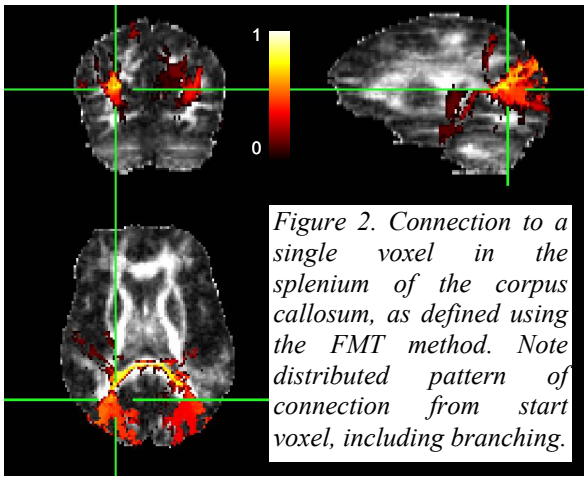

Figure 2. Connection to a single voxel in the splenium of the corpus callosum, as defined using the FMT method. Note distributed pattern of connection from start voxel, including branching.

2.3. Probabilistic Methods

The voxel fibre orientation functions used in distributed tracking methods allow connection probability, or the confidence with which a connection has been identified, to be estimated if these distributions are defined in terms of fibre orientation probability (producing fibre orientation probability density functions (PDFs)). One method for generating PDFs is by employing a model of the expected dispersion of fibre orientation information due to noise (9, 17, 10, 18). Figure 3 shows a set of simulations indicating the degree of dispersion in fibre orientation expected due to noise at a range of tensor fractional anisotropy (FA) levels.

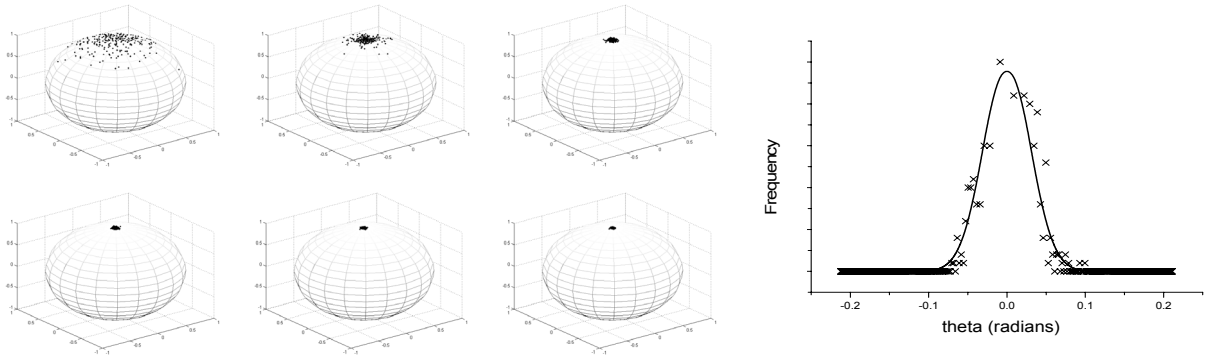

Figure 3. Left: dispersion in fibre orientation measurements due to noise over a range of FA. Dispersion is greatest at low anisotropy. True fibre orientation is along vertical axis. Right: fibre orientation Dispersion at FA = 0.78. The Gaussian function fitted to data indicates normally-distributed dispersion, allowing the definition of an easily-parameterised PDF. For more detail see Parker & Alexander 2003.

Another class of distributed method involves the use of Monte Carlo, or probabilistic, streamline approaches (9, 10, 19). These methods (closely related to the Monte Carlo simulated diffusion methods) use PDF definitions as above to define a distribution of possible streamline propagation directions at each point in the brain. Streamline propagation is then repeated (typically 1000 – 10000 times from each start point (20)), with random sampling of these distributions on each iteration. Again, the number of times that each voxel in the brain encountered by a streamline is recorded, and this is used to define the probability of connection.

Care is required in the interpretation of connection probability. A model of the diffusion phenomenon is required (such as the diffusion tensor) to tell us how to infer fibre orientation information from a DWI acquisition. The PDF describing the likely distribution of possible fibre orientations at any given point in the brain is subsequently generated using this model. A measure of probability that two brain voxels are connected may be generated if firstly the model describing the relationship between the observed DWI signal and fibre orientation is accurate, and secondly if the connection probability is defined as the path integral of the local fibre orientation PDFs. In practice our knowledge of the relationship between DWI observations and underlying fibre orientation distributions within

an imaging voxel is poor, with the exception of identifying the dominant fibre orientations; therefore the first condition is not in general met. However, even with this significant caveat in place, a large amount of progress has been made in deriving probabilistic maps of brain connections that answer the question, ‘‘how confident can I be that a route of connection, as represented by my model of the relationship between fibre orientation and my DWI data, exists between point A and point B in the brain?’’

3. The Tensor and Beyond

3.1. Limitations of the Diffusion Tensor

The diffusion tensor was the first model applied to DWI data to estimate the orientation of fibre bundles (3) and most fibre tracking methods have until recently relied on this information. However, a number of authors have demonstrated that there are numerous brain regions in which the diffusion tensor is a poor model of the measured diffusion signal (21-24). This is because the tensor can identify at most a single dominant fibre orientation, whereas in many parts of the brain more complex fibre architecture is present. These situations occur when fibres cross (for example where the corticospinal tract, running superior–inferior, encounters callosal fibres running left–right in the centrum semiovale), diverge/converge (for example in the corona radiata) or display tight curvature (for example in the optic radiation). In such cases more sophisticated models of the observed diffusion characteristics are required.

3.2. Incorporation of Complex Fibre Architecture

Models of complex fibre architecture that have been utilised for tractography include tensor mixture models (25, 10, 26), diffusion spectrum imaging (27, 28), PAS-MRI (18), spherical deconvolution (29), and q ball (30, 31). All tracking methods that use the diffusion tensor may be extended to cope with multiple fibre populations. For example, streamline tracking and streamline-based probabilistic methods may be extended to multiple fibre populations by the incorporation of a simple choice regarding which population to follow based on the orientation of the previous propagation direction (25, 10, 28, 18, 31). Figure 4 shows an example of probabilistic tracking from the parahippocampal gyrus using q ball to derive up to 4 possible fibre orientations per voxel, as described in (31).

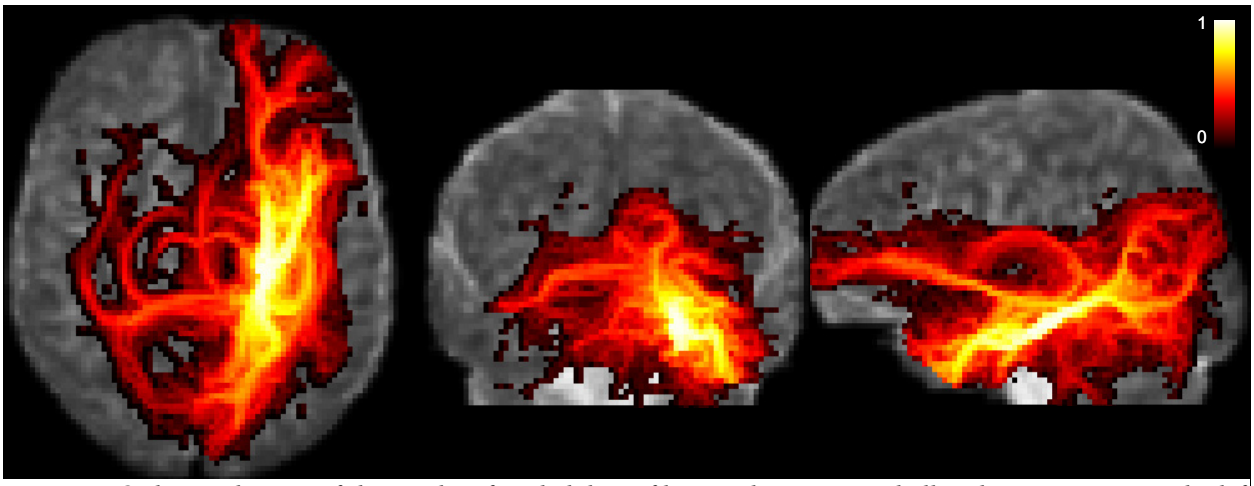

Figure 4. Orthogonal views of the results of probabilistic fibre tracking using q ball with a start point in the left parahippocampal gyrus. Probabilistic tracking output is shown as a projection in each view.

4. Quantification using Fibre Tracking

Much work using fibre tracking has to date focussed on qualitative assessment of fibre tract trajectories. This has a number of potentially useful applications, such as for surgery planning (see for example (32)) and for understanding gross anatomy (see for example (4, 33)). However, tractography may also be used to derive quantitative information.

4.1. Tract Volume and Path Density Measurements

Fibre tracking may be interpreted as a segmentation procedure. The result of this segmentation is volumes that represent specific fibre tracts. Measurement of the volume of these fibre tracts is therefore possible. Figure 5 shows an example of tract volume measurements in the left and right hemisphere of fibre tracts associated with language function, showing clear lateralisation to the left hemisphere in a group of right handed volunteers (34, 26). An alternative approach, when using a streamline-based method, is to measure the number of streamlines that are

associated with a specific tract. Similar connection lateralisation information has been derived using this approach (35).

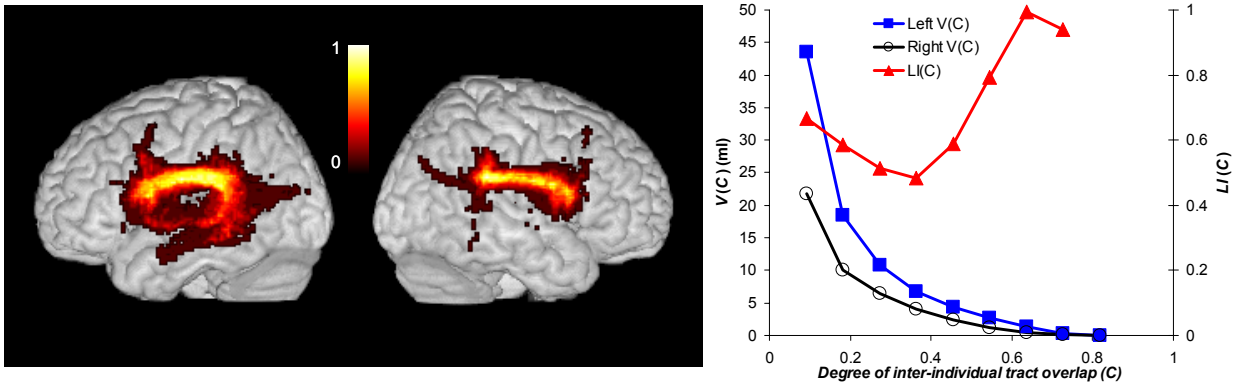

Figure 5. Left and right connecting volumes associated with Broca's and Wernicke's areas. The maps on the left show the degree of overlap (C) across the group of individual tracking results (scaled between 0 and 1). The graph on the right summarises the volumes at each value of C for the left and right hemispheres, in addition to the lateralisation index (LI).

4.2. Tract Microstructure Measurements

Isolation of a specific tract using tractography allows interrogation of the tract for evidence of damage. Indices such as diffusion anisotropy, relaxation times, and the magnetisation transfer ratio may all be measured within the tract, which provides a degree of network specificity unavailable without tractography. This may be of interest in understanding the effects of pathology – for example the effects of multiple sclerosis lesions on the microstructure of the motor pathways (36). The anisotropy of fibre bundles isolated with tractography has also been shown to relate to the amplitude of signal change associated with functional activation in related cortical areas (20).

4.3. Connection Probability Matrices

Probabilistic tracking methods allow the confidence of connection between regions to be established. Given multiple inter-regional tracking experiments it is possible to derive connection matrices that record each measured point-to-point or region-to-region connection probability (27, 37). Recent work has demonstrated that this information allows specific identification of cortical functional regions according to their connection profile, generating an independent means by which certain functional areas may be identified within the grey matter (37).

Acknowledgements

I am grateful to Derek Jones for providing Figure 1.

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